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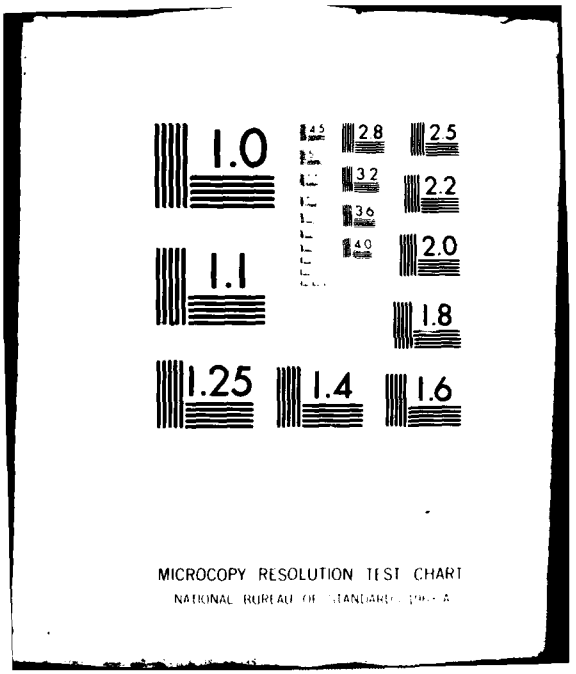
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ACUTE OPTIC NEURITIS: PROGNOSIS FOR THE DEVELOPMENT OF MULTIPLE SCLEROSIS

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December 1979

USAF SCHOOL OF AEROSPACE MEDICINE
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The literature was reviewed in regard to acute optic neuritis: prognosis for the development of multiple sclerosis, with specific reference to our flying population. Two major factors were found that influence the large discrepancy in statistics. The first was that the patient population, in many series, was preselected and not prospective, causing a higher incidence of later multiple sclerosis. The second factor was the definition of multiple sclerosis used by various groups. When strict criteria were followed for such definition, many of the apparently dissimilar series were, in fact, quite similar. Two series →

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20. ABSTRACT (continued)

which most closely parallel our flying population are reviewed in detail. Both series suggest a very low incidence of later development of multiple sclerosis in patients affected with acute optic neuritis. This finding leads us to conclude that an incidence of 13% to 17% (calculated on life tables) most accurately represents the risk that our flyers who are afflicted with optic neuritis will later develop multiple sclerosis.

CONTENTS

ACUTE OPTIC NEURITIS: PROGNOSIS FOR THE DEVELOPMENT OF MULTIPLE SCLEROSIS

INTRODUCTION

Although generally agreed that acute optic neuritis in adults may be the first sign of multiple sclerosis, wide variation exists in the reported incidence of multiple sclerosis developing after an acute optic neuritis. Kurland et al. (4) found that 13% of U.S. Army servicemen with optic neuritis, followed up for 12 to 18 years, developed multiple sclerosis--whereas Bradley and Whitty (2), at Oxford, found that 51% of their patients later developed definite or probable multiple sclerosis. Other figures, such as those by Lynn (5), ranged as high as 85%. Many of the reports include patients with other signs of multiple sclerosis at the onset of optic neuritis, and therefore do not contribute to resolving this problem.

The purpose of this Review is to clarify the prognosis of patients with acute optic neuritis with regard to the later development of multiple sclerosis. This issue is especially pressing when one considers the number of flying personnel who have had one or two attacks of isolated optic neuritis. If, in fact, 85% of such patients went on to develop multiple sclerosis, this percentage would present a significant threat to mission-completion. On the other hand, if the risk of such patients developing multiple sclerosis is as low as 11% to 15%, this percentage may represent an acceptable risk.

The question really is: Can one derive any useful conclusions from data in which the risk of developing multiple sclerosis after an acute attack of optic neuritis ranges from as little as 11.5% to as much as 85%? We think the answer to this question is "Yes."

BASIC ISSUES

The great disparity among different studies really revolves around two central issues: First, patient selection and the population from which the patients were drawn; and, second, the definition of what constitutes multiple sclerosis. Through understanding these two basic issues, we can reconcile the results obtained from various studies.

Patient selection and the population from which patients are drawn is obviously a very important issue. As has been shown here at the USAF School of Aerospace Medicine, certain electrocardiographic abnormalities previously felt to be pathologic in a hospital population are now well established to be benign in nature when considered in the context of otherwise healthy individuals (9). Delineation of any temporal relationship of optic neuritis to multiple sclerosis requires consideration of three factors: (a) the proportion of multiple sclerosis cases presenting with optic neuritis and other concurrent neurologic dysfunction; (b) the proportion of cases of multiple sclerosis in which optic

neuritis develops; and (c) the frequency with which optic neuritis occurs alone or may be a harbinger of multiple sclerosis. As for the first factor (a), accurate information can be obtained retrospectively to document the initial symptoms of multiple sclerosis in a well-defined series. The second factor (b) may also be solved by retrospective analysis of a series of well-documented cases of multiple sclerosis in patients who have had an extended clinical course.

Both issues (a) and (b) are best approached by total ascertainment of all cases on a circumscribed population to insure that a total spectrum of disease is studied. Where this survey has been made carefully, most data tend to agree that 15% of patients with diagnosed multiple sclerosis initially presented with optic neuritis. Moreover, from 27% to 37% of patients with multiple sclerosis showed evidence of optic neuritis during the course of their disease. While statistics vary on this issue, they are in general comparable within a few percentage points. The problem arises when one tries to resolve the third factor (c), the frequency with which optic neuritis occurs alone or may be a harbinger of multiple sclerosis. This question is best answered not by a retrospective study but by a prospective study of all cases of optic neuritis in a population over a follow-up period during which the cases of multiple sclerosis are likely to develop.

DISCUSSION

Since the results of published series on optic neuritis have provided multiple sclerosis frequencies varying between 11.5% and 85%, studies based on well-documented cases of optic neuritis in a defined population are less likely to encounter bias due to problems of selection. This is, of course, the problem with many of the studies in which a high incidence of multiple sclerosis is based on retrospective studies of hospital files (7, 11). As an example, in Hutchinson's paper (3), the patients constituting the series were all patients with a diagnosis of acute optic neuritis or multiple sclerosis initiated by an episode of acute optic neuritis during the 1960 - 1974 period. As can be seen from this patient population, we are dealing: first, with a retrospective study; and, second, with a preselected group of patients, including those with multiple sclerosis who presented with optic neuritis, automatically selected for a high incidence of multiple sclerosis following the development of optic neuritis. Furthermore, all these patients were reviewed, based on the hospital records of a referral center. An often quoted study by Bradley and Whitty (2) is based on 66 patients who had been referred to the Department of Neurology of the United Oxford Hospitals in England. Again, definite patient selection occurred here, even though the authors felt this study represented an unbiased selection.

The two studies which come closest to a prospective unbiased patient selection also have the lowest incidence of multiple sclerosis developing after an acute optic neuritis. The first, by Kurland et al.(4),

actually is the largest study reviewed. This report, from the National Institute of Neurologic Diseases and Blindness, was done in cooperation with the Veterans Administration and the National Academy of Sciences, National Research Council. The report was based on a review of 428 original Army records (1942-1948) in which the diagnosis of optic neuritis had been made. This review was made without knowledge of the subsequent medical history of these patients. Strict criteria were used, and the number of eligible patients with optic neuritis of unknown cause was found to be 183. Within this group of 183, an especially selected sample was made of those 52 patients with acute unilateral retrobulbar neuritis (the entity most likely to progress to multiple sclerosis). Records were examined on the total group, through 1958, and revealed only 18 cases of diagnosed multiple sclerosis. The authors at this point felt that, because many patients did not have neurologic follow-up, many patients with multiple sclerosis may well have been missed. Arrangements were then made for examination of all living members of the group of 183. Only 10 cases lacked specific neurologic follow-up; and, of these: 2 had suffered early death, not related to multiple sclerosis; 2 were on active duty, and their routine records were negative; and 5 refused examination. In one of the patients, examination could not be arranged and the record review was negative. During this time, 108 patients who had not been evaluated neurologically initially had follow-up examinations. In all cases with neurologic signs or symptoms, detailed abstracts were reviewed by a panel of neurologists; and these cases were classified as definite, or possible--or not multiple sclerosis. The diagnosis of definite multiple sclerosis consisted of three factors: the first was objective evidence of impairment of two or more parts of white matter; the second was either two or more attacks or continuous progression over an interval of six months; and the third was no evidence of other neurologic disease. Patients were classified as possible multiple sclerosis if equivocal evidence was found of nonvisual neurologic symptoms or signs. After careful review of all cases, 45 of the accepted 183 cases had some neurologic dysfunction. All of these were reviewed in detail, and only 21 were judged to have definite multiple sclerosis; 3 were considered possible; and the rest were felt to represent no disease.

When one considers strictly the definite cases of multiple sclerosis, only 11.5% of the 183 patients had the disease at the end of the 12- to 18-year follow-up; and, 13.1% of this group had either definite or possible multiple sclerosis. These statistics were identical for the selected group of 52 patients who were felt most likely to develop multiple sclerosis.

Another important factor, in this study and in others, is that the majority of nonvisual neurologic involvement (in this case, 11 out of 21) occurred within the first 2 years of follow-up. Factors not considered significant in later development of multiple sclerosis were unilateral vs. bilateral optic nerve involvement, papillitis vs. retrobulbar neuritis, and severity of visual loss. The only positive correlations

between patients presenting with optic neuritis and later developing multiple sclerosis were unequal pupils in 6 out of 19; those with 20/20 vision at induction had a lower chance of developing multiple sclerosis (7 out of 195); and patients with 12 or more years of education had an increased risk of developing multiple sclerosis. None of these correlations was felt to be statistically significant.

One fact of great interest was that, of 108 patients who were initially lost to follow-up and finally examined neurologically, only one case of multiple sclerosis was found which was not known before these examinations took place. This finding, of course, is to be expected if optic neuritis is generally an isolated phenomenon and not related to neurologic disease. If one limited his review to patients with optic neuritis who returned within the 12- to 18-year period complaining of further difficulty, one would, of course, have a much higher incidence of multiple sclerosis following optic neuritis.

Percy et al. (8) carried out a prospective study of patients with optic neuritis in Olmsted County, Minn., between 1935 and 1964. This study was limited to residents of the area and did not include patients referred to the Mayo Clinic from other areas. The medical indexing and records retrieval system, used not only at the Mayo Clinic but at all surrounding medical facilities in Olmsted County, assured the identification of practically all local persons in whom an illness had been diagnosed and for whom consultation (by internist, neurologist, ophthalmologist, or other specialist) was likely. From this group, 92 individuals were identified: 54 cases were felt to satisfy the criteria of residency; of these, 24 had no specific etiology for their optic neuritis; out of the 24, only 4 developed multiple sclerosis over a follow-up period averaging 18 years. When life tables were applied to these data, the chance of developing multiple sclerosis after an attack of idiopathic optic neuritis was found to be 17%. The criteria for the diagnosis of multiple sclerosis were the same as those used in the Kurland study (4).

Both the difference in patient selection and the definition of what constitutes multiple sclerosis become evident when one reviews McAlpine's (6) series of 214 patients with multiple sclerosis, all seen at Middlesex Hospital. He defined definite multiple sclerosis as a history of optic neuritis or paraesthesiae that cleared, followed by a relapse with an addition of the presence of pyramidal tract signs or other signs of multiple CNS lesions. He called multiple sclerosis probable if, during the original attack, clinical evidence of multiple lesions was found; or if, during follow-up, fresh lesions were absent but a tendency to variability was apparent in the pyramidal and other signs. These signs could be extensor plantar responses, nystagmus, or optic pallor. A second probable group were those patients with a history of one or more acute attacks of optic neuritis accompanied by, or followed by mild pyramidal signs with subsequent evidence of relapse. Those who were

considered possible multiple sclerosis had a history which fell under the criteria used for probable, but with unusual features or a paucity of signs.

Such a study, based on hospital records of patients with multiple sclerosis, is obviously biased when one is trying to determine the percentage of patients developing multiple sclerosis after an isolated attack of optic neuritis. The diagnostic criteria used by McAlpine (6), which are the basis for most English studies, are much less demanding than those of Kurland (4). The other large English study, by Bradley and Whitty, points out that the diagnosis of definite multiple sclerosis based on McAlpine's criteria has been regarded by many as too lax, especially for use in therapeutic trials (2). They also point out that the label of probable multiple sclerosis is a far less certain one--and, if accepted mechanically, patients with cervical myopathy, stroke, and many other conditions would be included. Bradley and Whitty (2) felt that even a careful history might not always exclude such patients. They further commented that, while following these criteria, they found 20% of patients fell into the definite group and 31% into the probable group. They felt, however, that a skeptical neurologist might have made the diagnosis in fewer patients, especially in regard to the probable group (2).

A brief review of the Bradley and Whitty series is in order, since it has a large number of patients followed over a mean period of 10.2 years (2). The study reviewed 66 patients presenting to the Department of Neurology at Oxford with acute optic neuritis. Definite multiple sclerosis declared itself in all but one patient within the first four years of follow-up. They also found that the frequency of multiple sclerosis developing in patients with normal and abnormal cerebrospinal fluid (CSF) at the onset of optic neuritis was the same; i.e., a patient may have an abnormal CSF and never develop multiple sclerosis, or a patient may have a normal CSF gamma globulin at the onset and eventually develop multiple sclerosis. Pain on eye movement also had no direct bearing on the later development of multiple sclerosis.

OBSERVATIONS

Several interesting factors arise from this study. Those categorized as definite multiple sclerosis, even in this select population, only accounted for 20% of the patients. The other 31% considered probable multiple sclerosis were regarded in a skeptical manner even by the authors. What is most important about this series is that, in spite of the fact that the series is selected, it is a prospective study in which (after 10.2 years) 91% of the patients have been completely unrestricted in their activities. Even when those patients with multiple sclerosis were considered, 64% were unrestricted--as opposed to 27% unrestricted in other series of multiple sclerosis patients, who did not have optic neuritis at onset. Thus, statistically, the definition of multiple sclerosis is quite important. If strict criteria were applied, the fact

becomes apparent that even in selected series the incidence of later development of definite multiple sclerosis is much lower than the overall statistics would indicate--in this series, a 20% incidence.

The most striking finding in all of these series is that patients who had an onset of multiple sclerosis with optic neuritis in general have a much more benign course than those with other presentations. In fact, some have regarded onset with optic neuritis as a good prognostic sign in multiple sclerosis. Also very pertinent in Bradley and Whitty's series is that 91% of their patients were completely unrestricted at the time of follow-up, which averaged 10.2 years (2). Many of the patients, from a functional point of view, were not compromised by their disease. In fact, McAlpine, who had a long-term study of 214 patients, selected 78 patients who were unrestricted--the mean follow-up in these cases was 18.2 years (6). The presenting symptoms were paraesthesiae in 50%, acute retrobulbar neuritis in 36%, and motor weakness in 34%. When these were the presenting signs, McAlpine felt that the outlook of the disease was much better.

Finally, a comment is in order about the cerebrospinal fluid findings in patients who present with optic neuritis and later develop multiple sclerosis. In the early studies of Bradley and Whitty, no prognostic significance could be attached to abnormal CSF in regard to development of multiple sclerosis (2). Abnormal spinal fluid was found in patients who later developed multiple sclerosis and also in those who did not. Similarly, normal spinal fluid was found in those who later developed the disease, and also in those who did not. More recently, Sandberg-Wollheim did studies on the CSF in relation to the clinical course in 61 patients with acute monosymptomatic optic neuritis (10). They found that, at the beginning of the disease, a mononuclear pleocytosis was noted in 51% of the patients, an elevated IgG in 18%, and an oligoclonal IgG distribution in 41%. No correlation in time existed between the appearance of new symptoms and the CSF changes. In 6 patients with normal CSF and in 4 patients with only mononuclear pleocytosis at the onset of the disease, the IgG pattern became oligoclonal on electrophoresis during the follow-up period, although these patients had no further symptoms or signs of disease. Of the 11 patients who developed multiple sclerosis, only 6 had CSF abnormalities at the onset; but, in the remaining group of unaffected optic neuritis patients, 12 had CSF abnormalities at the onset. Six of the patients had an oligoclonal IgG pattern, but none developed subsequent multiple sclerosis.

Aronson has discussed the difficulty of using HLA-3 or HLA-7 along with measles antibodies as a predictive factor in patients with optic neuritis (1). He does point out that patients who have an LD-7a are theoretically at a 15 times greater risk of developing multiple sclerosis. At the present time, chemical studies of the CSF are, at best, suggestive--and in no way should be considered of definite prognostic value, other studies notwithstanding (12).

When all factors are considered, given our healthy flying population, the statistics that more closely approximate their real life situation are those in the studies of Kurland (4) and Percy (8), both of which deal with a defined population not preselected for neurologic involvement. In fact, our population may be biased, similar to that of Kurland (4), in that most flyers are male--while most patients with optic neuritis who later developed multiple sclerosis are predominantly females, in a ratio of 2.7 to 1 in some studies. When one considers the need for a prospective study as well as an understanding of what is meant by the definition of multiple sclerosis, it becomes obvious that for our purposes a much lower incidence of optic neuritis patients developing multiple sclerosis is likely in our flyers. A figure of 15% to 17% would be most reasonable. As already mentioned, even this 15% to 17% of flyers who go on to develop multiple sclerosis have a much better prognosis than do most other patients with this diagnosis.

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